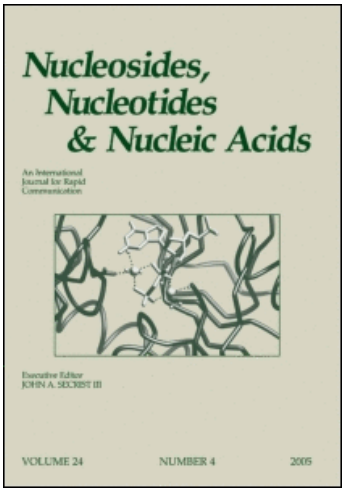

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Synthesis and Receptor Affinity of Polysubstituted Adenosines

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SYNTHESIS AND RECEPTOR AFFINITY OF POLYSUBSTITUTED ADENOSINES

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ABSTRACT: In a search for potent and selective adenosine agonists it has been found that 2-hexynyladenosine-5'-N-ethyluronamide (HENECA) displays high affinity at rat A_{2A} receptor combined with a good A_{2A} *vs* A_1 selectivity. The finding that HENECA shows good affinity also for A_3 receptors prompted us to investigate the effect of various substituents in different positions of this molecule.

INTRODUCTION

Investigating new and selective adenosine receptor ligands it has been found that 2-hexynyladenosine (HEAdo, **1**) is endowed with high affinity for adenosine receptor.[1] The introduction of an ethylcarboxamido group at the 5'-position led to 2-hexynyladenosine-5'-N-ethyluronamide (HENECA, **2**) which displays high affinity at rat A_{2A} receptor combined with a good A_{2A} *vs* A_1 selectivity.[2] HENECA was also found to possess good affinity for A_3 receptor subtypes.[3] Furthermore, NECA analogues containing N^6 arylcarbamoyl groups have shown high affinity at rat A_1 and A_3 adenosine receptors.[4]

These findings prompted us to investigate the effect of different substituents in N^6- and 5'-positions of HEAdo.

The synthesis of the new compounds will be published elsewhere.

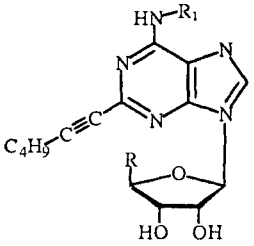
RECEPTOR AFFINITY

All the synthesized compounds were evaluated at the human recombinant adenosine receptors, stably transfected into Chinese hamster ovary (CHO) cells, utilizing radioligand binding studies (A_1, A_{2A}, A_3) or adenylyl cyclase activity assays (A_{2B}) (Table 1).[5]

Preliminary results showed that the 2-hexynyl adenosine (**1**) showed high affinity for A_1, A_{2A}, and A_3 receptor, while the affinity for the A_{2B} subtype was very low (EC_{50} > 100 μM). The substitution of the hydroxymethyl group in the 5'-position with an ethylcar-

boxamido led to a compound (HENECA, **2**) with comparable affinity at A_1 and increased affinity at A_{2A}, A_{2B}, and A_3 receptors. Replacement of the ethyl group of the carboxamide by a cyclopentyl ring (**3**), as well as substituents in the N^6 position (**4**, **5**, **6**), brought about a decrease of the affinity at all the receptor subtypes. These data demonstrate the negative interdependence, in terms of affinity, of these substituents at C^2- and N^6-positions of the purine moiety.

Table 1. Affinities of selected adenosine derivatives in radioligand binding assays at human A_1, A_{2A} and A_3, and in adenylyl cyclase assays at human A_{2B} adenosine receptors.



			Ki or EC_{50} (nM)			
Cpd	R	R_1	Ki (A_1)	Ki (A_{2A})[a]	EC_{50} (A_{2B})[b]	Ki (A_3)[c]
1	$HOCH_2$	H	45[d]	11	>100,000	7.7
2	EtNHCO	H	60[d]	6.4	6,100	2.4
3	cC_5H_9NHCO	H	403[d]	49	>100,000	16
4	EtNHCO	cC_5H_9	73[d]	178	>100,000	65
5	EtNHCO	3-Cl-Ph-NH-CO	2,000[e]	>10000	>100,000	36
6	EtNHCO	4-CH_3O-Ph-NH-CO	428[e]	>10000	>100,000	57

[a]Displacement of specific [^{3}H]NECA binding in CHO cells, stably transfected with human recombinant A_{2A} adenosine receptor, expressed as Ki (nM). [b]Measurement of receptor-stimulated adenylyl cyclase activity in CHO cells, stably transfected with human recombinant A_{2B} adenosine receptor, expressed as EC_{50} (nM). [c]Displacement of specific [^{3}H]NECA binding in CHO cells, stably transfected with human recombinant A_3 adenosine receptor, expressed as Ki (nM). [d]Displacement of specific [^{3}H]DCPX binding in CHO cells, stably transfected with human recombinant A_1 adenosine receptor, expressed as Ki (nM). [e]Displacement of specific [^{3}H]PIA binding in rat brain membranes (A_1) expressed as Ki (nM).

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